



Review article

Cardiovascular toxicity of novel psychoactive drugs: Lessons from the past

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ABSTRACT

The long use of ephedrine, amphetamines, cocaine, LSD and more recently 3,4-methylenedioxy-N-methylamphetamine (MDMA; "Ecstasy") allows us to predict with some confidence what cardiovascular risks are likely to be associated with novel psychoactive substances (NPS). Once the probably multiple biological activities of a compound are known it is possible to define the likely risks of cardiovascular toxicity. Agonists of 5-HT_{2A} receptors or alpha-adrenoceptors may cause vasoconstriction and tissue ischemia. Drugs which have agonist affinity for 5-HT_{2B} receptors will probably promote heart valve fibrosis leading to heart failure. Compounds that interfere with uptake of dopamine or 5-hydroxytryptamine (5-HT) are likely to also have effects on noradrenergic neurotransmission and lead to sympathomimetic effects on the heart and vasculature. Drugs that cause dopamine release, or inhibit uptake are likely to be addictive and lead to chronic use. Other drugs (particularly the so-called empathogens) are associated with weekly usage in social settings; over time such use can lead to cardiovascular harm. Defining which of these effects NPS have is an important element of predicting the harm they may cause and informing those appointed to introduce regulations to control them.

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1. Introduction

Several classes of recreational drugs that are taken primarily for their diverse effects on the central nervous system have additional effects on the heart and vasculature which contribute to morbidity and mortality. Illicit drugs such as cocaine and amphetamines which have a long history of use/abuse are clearly associated with

increased risks of cardiovascular complications such as myocardial infarction and stroke (see below). Indeed, the use of some licit drugs with similar mechanisms of action – such as pseudoephedrine – are also associated with cardiovascular risks and dispensed with caution. There is now a subset of recreational drug users who shy away from illicit drugs, seeking alternatives which are legal only because they are sufficiently novel to not have been considered for regulation by authorities (Hill and Thomas, 2011). Apart from user reports (of uncertain veracity), the pharmacological and toxicological properties of some of these compounds are virtually unknown. Structurally novel 'legal highs' (or novel psychoactive substances; NPS) are appearing at a rate of 20 or more per year (European Monitoring Centre for Drugs and Drug Addiction, 2011). The unknown pharmacodynamic, pharmacokinetic and toxicological properties of such compounds represent a significant challenge to authorities tasked with preventing public harm. The speed with which purveyors of such compounds identify

Abbreviations: 2-CB, 4-bromo-2,5-dimethoxyphenethylamine; 5-MeO-DIPT, 5-methoxy-N,N-diisopropyltryptamine; 5-HT, 5-hydroxytryptamine; BZP, benzylpiperazine; CNS, central nervous system; DAT, dopamine transporter; LSD, lysergic acid diethylamide; mCPP, 1-(3-chlorophenyl)piperazine; MDMA, methylenedioxymethamphetamine; MDPV, methylenedioxypropylvalerone; NET, noradrenaline transporter; NPS, novel psychoactive substance; SERT, serotonin transporter; TCB-2, (4-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine; TFMPP, 1-(3-trifluoromethylphenyl)piperazine.

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and produce novel substitutes after regulations are put in place is a further challenge in this field. In this review we outline some of the aspects of NPS cardiovascular toxicity that might be predictable, based on our understanding of drugs with similar mechanisms of action.

The cardiovascular effects of recreational drugs are – to some extent – predictable because the receptors and transporters on which they act are located both in the central nervous system and in the periphery. There is a limited palette of molecular targets in the central nervous system upon which drugs that produce the varied desired effects can act. Some classes of drugs are unlikely to have a vascular risk profile and are not considered in depth in this review. For example, cannabinoids produce a predominantly vasodilator response (Randall et al., 2004), and are unlikely to cause cardiovascular complications. Others, acting on serotonergic, dopaminergic or noradrenergic systems are far more likely to induce vasoconstriction and/or tachycardia and arrhythmia. The most hazardous compounds are likely to be those that have some central dopamine-releasing activity – carrying higher risks of addiction and chronic abuse – combined with peripheral cardiovascular effects which are likely to be toxic after such continued abuse. We have experience with a sufficient number of licit and illicit drugs to be able to assess – with some confidence at least – what the potential risks of NPS might be once their pharmacological activities are characterised. Because these drugs often share structural similarities with several such bioamines, their effects are rarely limited to a single receptor or transporter. Hence it is difficult to decide whether, for example, some of the hallucinogenic amphetamines should be characterised as hallucinogens or CNS stimulants, phenethylamines or tryptamines. We have structured this review around the different endogenous signalling systems, rather than classes of chemicals, or the potentially mixed effects they have on the body to simplify an assessment of the cardiovascular risks that might be predicted for molecules with mixed affinities and efficacies.

2. Serotonergic drugs

Serotonin (5-hydroxytryptamine (5-HT)) takes its name from the vasoconstrictor effects it was first reported to elicit. It was originally discovered as a platelet-derived vasoconstrictor factor (reviewed by Green, 2008; Watts, 2002) and it was some years before its role as a central nervous system neurotransmitter was described (Green, 2008). The bulk of the 5-HT present in the body is stored in gastrointestinal enterochromaffin cells which release 5-HT when triggered by a variety of stimuli. Some of the spillover of 5-HT is taken up and stored by platelets, which possess the same uptake mechanisms as neurons, the other significant source of 5-HT in the body. It is probable that the physiological role of vascular 5-HT receptors is to mediate vasoconstriction to support a clot and limit blood flow. Activation of this system throughout the body has a profound vasopressor effect. Indeed, 5-HT induced vasospasm has been implicated in the pathogenesis of circulatory disorders such as migraine and Raynaud's phenomenon (Kaumann and Levy, 2006). Unsurprisingly, 5-HT receptors were for a long time considered to be a potential target for novel hypertensive drugs. Indeed, the 5-HT_{2A} receptor antagonist ketanserin was an effective antihypertensive, but was withdrawn due to associations with torsade de pointes (Nagatomo et al., 2004). Similar antagonists with fewer cardiac effects have been produced, but have been surpassed by other classes of anti-hypertensive agents and have more limited indications.

The history of ergotism warns of the potential cardiovascular risks of serotonergic agents (Haarmann et al., 2009). The fungus *Claviceps purpurea*, which has periodically infected cereal crops over the centuries, contains a variety of alkaloids which act at bioamine receptors, particularly 5-HT receptors (Schiff, 2006). Ingestion of bread made from infected crops produced profound peripheral vasoconstriction that underscored all of the pathological signs of what came to be known as St Anthony's Fire. Victims writhed from the pain of the

extensive ischemic damage to their extremities and many ultimately died. Later, ergot preparations came to be used medicinally for inducing abortions and later for preventing post-partum bleeding when the uterus fails to contract sufficiently. One constituent of ergot, ergometrine, is still occasionally used for this purpose today (Basket, 2000; Basket, 2004) and there have been occasional reports of iatrogenic ergotism in the literature (e.g. Ibrahim et al., 2008), despite the relative selectivity of this compound for uterine over vascular smooth muscle. Ergometrine has also been used for many years – and with caution – as a provocation test for coronary artery vasospasm (Siegel, 2010). The precise receptor pharmacology of ergometrine is uncertain – the compound has affinities for receptors for 5-HT as well as those for catecholamines. It is not surprising then, that NPS which have 5-HT agonist properties have the potential to harbour similar, additional cardiovascular risks.

There are at least 14 receptors for 5-HT, but the two main receptors expressed by vascular smooth muscle are 5-HT_{2A} and 5-HT_{1B} (see Kaumann and Levy, 2006). The relative contributions of each receptor vary between vascular beds. For example, the high expression of 5-HT_{1B} receptors by cerebral arteries was the original target of the 'triptan' class of drugs (5-HT_{1B/D} agonists) which are used to promote vasoconstriction in migraine, but also activate 5-HT_{1F} receptors on perivascular nerves (Mehrotra et al., 2008). Since the coronary circulation has a less significant population of 5-HT_{1B} receptors, with 5-HT_{2A} predominating, this class of drug is relatively free of coronary side-effects. However, triptans are generally prescribed with caution in patients with underlying heart conditions because of the possible risk of coronary vasoconstriction and this may be why they appear to have a good safety profile (Bigal et al., 2009). The pharmacology of an older (but still utilised) drug for migraine makes an instructive example of the complicated nature of cardiovascular 5-HT receptor pharmacology. Methysergide was originally introduced as a 5-HT antagonist to prevent what was considered the dominant role of 5-HT in migraine pathogenesis. Though still considered a 5-HT_{1/2} antagonist to this day, it seems likely that the active – and more potent and efficacious (Roon et al., 1999) – metabolite (methylergometrine/methylergonovine) mediates the beneficial effect of this drug possibly via agonist activity at 5-HT_{1B/D} or 5-HT_{1F} (Adham et al., 1993) receptors. CNS side-effects of methysergide (mild hallucination upon initial dosing is not uncommon) have always been a problem with its use in migraine prophylaxis; in the 1950s and 1960s it was found that methysergide was only 175 times less potent than LSD (the parent molecule) at producing similar CNS effects (Abrahamson and Rolo, 1965). Although the pharmacology of this compound has never been fully resolved, the activity of methysergide as a 5-HT_{1A} agonist (Newman-Tancredi et al., 1997) probably accounts for some of its CNS activity. The potent hallucinogen LSD, on the other hand, appears to act as a partial agonist of both 5-HT_{2A} and 5-HT_{1A} receptors (Halberstadt and Geyer, 2011; Passie et al., 2008), with effects via 5-HT_{2A} receptors predominating. In selecting NPS, many vendors appear to mine the scientific literature for potential 5-HT_{2A} agonist hallucinogens (e.g. 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT); Shulgin and Carter, 1980), with little consideration for what other properties these molecules may have. For example, 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT; "Foxy") elicits behavioural effects in animals similar to LSD via binding to 5-HT_{2A} receptors, although this compound has higher affinity for 5-HT_{1A} receptors (Fantegrossi et al., 2006), and also inhibits 5-HT uptake by blocking the 5-HT transporter SERT (Nagai et al., 2007; Sogawa et al., 2007). Similarly, there has been a recent increase in the use of fairly non-selective phenylpiperazine 5-HT agonists such as 1-(3-chlorophenyl)piperazine (mCPP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) (see Arbo et al., 2012; Hill and Thomas, 2011), which have been used experimentally for some decades (e.g. Lucki et al., 1989) and are now thought to also act via the SERT (Baumann et al., 2004; Eriksson et al., 1999). These rather old piperazine compounds – once potential anti-migraine drugs (Curzon and Kennett, 1990) – have such mixed affinities for 5-HT receptors and bioamine transporters that they

are generally distributed by vendors in combination with other drugs to make them palatable to users (see below).

Despite being a highly potent 5-HT_{2A} agonist and several decades of illicit use, there are only a few reports of LSD-related vascular complications (e.g. Raval et al., 2008), and very few deaths (e.g. Fysh et al., 1985) have been related directly to the toxicity of this drug (Henry, 1996; Passie et al., 2008). The vasoconstrictor properties of LSD were established over 30 years ago (Altura and Altura, 1981; Edvinsson et al., 1978), at a time when some thought that a component of the psychoactive effects of the drug might be related to cerebral ischaemia. However, although 20% of subjects in a blinded trial reported temporary, mild headaches after LSD ingestion (see Passie et al., 2008), reports of chest pains and other signs of severe peripheral vasoconstriction are scanty. Mild hypertension has been reported in several studies, but is thought to be driven by higher cortical centres, rather than direct effects on the cardiovascular system (reviewed by Passie et al., 2008), although relative contributions are difficult to disentangle. LSD-related presentations in emergency departments are principally due to anxiety and confusion associated with the psychedelic effect of the drug and treated with sedatives (Henry, 1996; Skinner and Thompson, 1992). Blaho et al. (1997) describe an interesting case series of such patients who presented in a single weekend after a concert by the band The Grateful Dead. Even inadvertent ingestion resulting in plasma concentrations five times higher (approximately 25 ng/ml) than a standard dose would produce was not associated with fatalities, although many of the patients described in this series were comatose at admission and may have died without medical support (Klock et al., 1973). A single case of lower limb ischaemia has been reported in recent years after probable LSD ingestion (Raval et al., 2008).

The mysterious cardiovascular safety of LSD and the observation that some 5-HT_{2A} receptor agonists do not in fact act as hallucinogens may in part be reconciled by recent developments in our understanding of receptor-effector signalling. The nature of 5-HT_{2A} receptor signalling is an interesting example of the phenomenon of functional selectivity: the ability of different agonists to recruit different cell signalling pathways via activation of the same receptor (Abbas and Roth, 2008; Cussac et al., 2008; McLean et al., 2006; Moya et al., 2007). Thus, some 5-HT_{2A}-selective agonists (e.g. 5-carboxamidotryptamine), are not hallucinogenic, while LSD (and others, e.g. 2,5-dimethoxy-4-iodoamphetamine) are, even though all of these molecules apparently interact with the same receptor. We have found similar evidence of selective activation signalling when examining potential vascular effects of hallucinogens. Thus, the putative hallucinogenic 5-HT_{2A} receptor agonist TCB-2 (Fox et al., 2010; McLean et al., 2006) appears to contract isolated arterial preparations almost exclusively via pathways that lead to smooth muscle cell depolarisation and opening of voltage-gated calcium channels (Fig. 1). In the same preparation 5-HT causes

contraction via activation of the same receptors, but these responses depend much less on voltage-gated calcium entry. Binding studies of NPS to 5-HT_{2A} receptors cannot provide useful information about the likely functional selectivity these compounds may have. Another paradox in the cardiovascular safety of LSD is that concentrations that cause cerebral vascular contraction in vitro (pEC₅₀ of approximately 8; Altura and Altura, 1981) are similar to the plasma concentrations that result from a standard 160 mg dose (approximately 5 ng/ml or 1.5×10^{-8} M; Upshall and Wailling, 1972). Perhaps the reason that symptoms such as headache and chest pain following LSD ingestion are relatively rare relates to the fact that LSD and other hallucinogenic 5-HT_{2A} agonists appear to act as partial agonists in many assays (e.g. Cussac et al., 2008; Moya et al., 2007), including isolated arteries (Altura and Altura, 1981; Fig. 1). The cardiovascular risks associated with NPS which have 5-HT_{2A} agonist properties will probably be determined by the extent and polarisation of their functional selectivity at this receptor. Those, like LSD, that are partial agonists that act principally to drive 5-HT_{2A} receptors to produce hallucinations are likely to be as harmless (to the cardiovascular system) as LSD itself unless taken in very high doses. However, compounds that also drive 5-HT_{2A} towards signalling that produces potent vasoconstriction might pose risks, both acutely and chronically. The “therapeutic ratio” of such drugs is also likely to be important. For example, the principally hallucinogenic 5-MeO-DIPT has been reported to be similar to LSD in its lack of significant vascular effects (Wilson et al., 2005), but has killed at least one user who overdosed (Tanaka et al., 2006). The single reported case of bromo-benzodifuranyl-isopropylamine (bromo-dragonFLY)-induced gangrene (see Psychonaut Web Mapping Research Project (2010a) for details of this Swedish case) given the short period of time this 5-HT_{2A} agonist drug has been available, suggests that some 5-HT_{2A} agonists might have more cardiovascular toxicity than others. A recent death through non-specific poisoning also points to a low therapeutic index for this compound (Andreasen et al., 2009). The non-specific toxicity of these compounds is an important consideration, given their high potency in some cases, and the crude methods employed by users to titrate doses. At present NPS vendors are marketing hallucinogenic 5-HT_{2A} agonists based on structure-activity data from scientific studies of experimental agonists. It is not surprising, perhaps, that this approach has had a limited toxicological toll. However, once the scientific literature has been mined completely, it is uncertain what strategies vendors will adopt in order to continue supplying legal hallucinogens. It is probably fortunate that most users of this class of abused drug do so infrequently and generally quite cautiously.

As the slow development of selective pharmacological agents by the pharmaceutical industry suggests, 5-HT receptor subtype-selective drugs are difficult to produce. Many of the NPS available are almost certainly active at multiple receptor subtypes, since they have not undergone rigorous pharmacodynamic screening and most currently licit

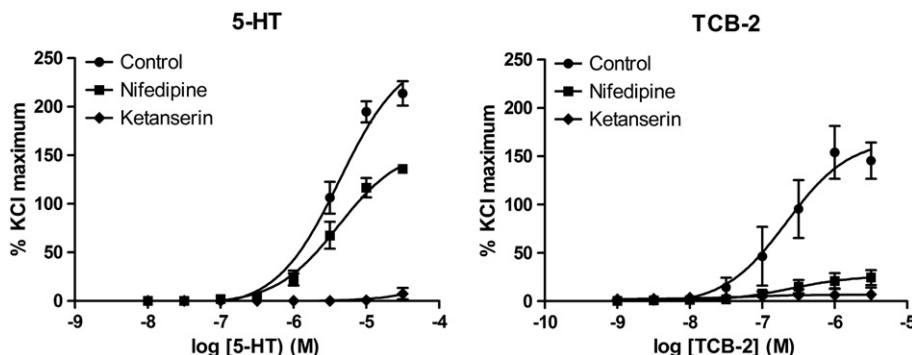


Fig. 1. Selective signalling by 5-HT_{2A} agonists in the rat aorta. 5-HT produces contractions which are abolished by the 5-HT_{2A} antagonist ketanserin, but minimally affected by blockade of voltage-gated calcium channels with nifedipine. On the other hand, the hallucinogen TCB-2 is equally sensitive to ketanserin and nifedipine ($n = 4$ each). Note that TCB-2 appears to be a partial agonist, another characteristic of 5-HT_{2A} agonist hallucinogens. Responses are expressed as a percentage of the contraction produced by elevating extracellular K⁺ to 68 mM.

and illicit drugs are promiscuous to some degree in any case. In addition to vascular 5-HT receptors described above, there is also concern that NPS might act on 5-HT_{2B} receptors expressed by heart valves. The association between carcinoid syndrome and heart valve fibrosis provides an insight into the effects of chronic non-selective cardiovascular 5-HT receptor activation. In carcinoid syndrome, enterochromaffin-like cells that have undergone metastasis to form tumours in the liver secrete excessive quantities of 5-HT (and other mediators) into the vena cava (see [Prejbisz et al., 2011](#)). This is thought to lead to the development of heart valve fibrosis via activation of 5-HT_{2B} receptors, since drugs such as the anorexic fenfluramine and the anti-Parkinson dopamine agonist pergolide which are also agonists for this receptor have had to be withdrawn due to similar associations with valvulopathy after long-term use ([Bhattacharyya et al., 2009](#); [Hutcheson et al., 2011](#); [Rothman and Baumann, 2002](#); [Rothman et al., 2000](#)). Similarly, long term use of methysergide (or the active metabolite methylergometrine) in migraine prophylaxis probably induced valvulopathy by activation of 5-HT_{2B} receptors ([Hutcheson et al., 2011](#)). By contrast, long term use of the anti-Parkinson dopamine agonist lisuride, also a 5-HT_{2B} antagonist, has not been associated with valvulopathy ([Hofmann et al., 2006](#)). The chronic use of NPS with similar affinity for 5-HT_{2B} receptors is likely to produce a similar effect, and screening for such activity is likely to help inform drug enforcement policy. Ecstasy (3,4-methylenedioxymethamphetamine; MDMA) is a case in point of a recreational drug with such a risk profile ([Setola et al., 2003](#)). The association between chronic Ecstasy abuse and heart valve fibrosis was only detected after the compound had been available to users for some time. A defined cardiovascular profiling programme might have predicted this earlier.

The arrival of Ecstasy on the recreational drug scene in the 1980s initiated a new interest in drugs that produce a novel mixture of effects. MDMA does not produce the same spectrum of CNS disturbances that are seen with related molecules such as mescaline and LSD ([Morton, 2005](#)). Rather, users report loss of inhibition and anxiety, with increased empathy for others (so-called empathogenic effects) as the pleasurable effects of MDMA. Administration of MDMA to animals causes a rapid increase in release of central 5-HT, and to a lesser extent dopamine and noradrenaline (see [Green et al., 2003](#) for an extensive review). The effect of MDMA on 5-HT uptake mirrors that of amphetamine on noradrenaline uptake (see below). MDMA is a false substrate for the uptake activity of the SERT, and also interacts with vesicular proteins to produce reverse transport, or dumping of 5-HT from pre-synaptic terminals ([Rothman and Baumann, 2002](#); [Green et al., 2003](#)). MDMA has some affinity for dopamine and noradrenaline transporters, but most of the subjective effects in humans can be blocked by serotonin transporter (SERT) inhibitors such as fluoxetine. MDMA has apparently relatively low affinity for the human 5-HT_{2A} receptor ([Setola et al., 2003](#)) possibly accounting for its limited hallucinogenic activity. From a cardiovascular point of view, the association between chronic MDMA use and heart valve fibrosis ([Bhattacharyya et al., 2009](#)) could be accounted for in two – not mutually exclusive – ways. Firstly, the effect of MDMA on 5-HT uptake by SERT on platelets might increase circulating 5-HT itself ([Yubero-Lahoz et al., 2011](#)), as in carcinoid syndrome. Secondly, MDMA has been shown to directly induce heart valve fibroblast proliferation in vitro via affinity for 5-HT_{2B} receptors ([Setola et al., 2003](#)). Valvulopathies have been observed in regular users, many of whom take MDMA only on weekends over a period of several years and might not consider themselves chronic users ([Bhattacharyya et al., 2009](#)). Many currently abused NPS are used in much the same way, and although affinity for 5-HT receptors has been described in some cases (e.g. [Nonaka et al., 2007](#)), specific receptor affinities and their efficacy as agonists are yet to be established.

After MDMA was made an illegal substance in most countries, 4-bromo-2,5-dimethoxyphenethylamine (2C-B or “Nexus”) became a popular substitute or adulterant in pills sold as Ecstasy ([Giroud et](#)

[al., 1998](#)). A recent study in Spain found that this compound is now actively sought by users as a product distinct from MDMA ([Caudevilla-Galligo et al., 2012](#)), but having similar empathogenic activity. Radioligand binding and functional studies have found 2C-B to be a 5-HT_{2A} agonist with a hallucinogen-like profile of cell signalling ([McLean et al., 2006](#)) and it has been shown to cause vasoconstriction via 5-HT_{2A} and alpha-adrenoceptors ([Lobos et al., 1992](#)). 2-CB is an equipotent inhibitor of SERT function, but is less potent at inhibiting noradrenaline transporters (NET) than MDMA ([Montgomery et al., 2007](#)). In one (analytically unconfirmed) case of 2C-B ingestion a patient presented with severe headache fully 48 h post-ingestion ([Ambrose et al., 2010](#)). Following admission, her condition declined after cerebral vasoconstriction worsened, causing irreversible brain damage. This case highlights the uncertain toxicological profile of NPS since vasospasm could be associated with the MDMA-like transport-inhibiting properties of 2C-B, or its efficacy as both a 5-HT_{2A} and alpha-adrenergic partial agonist ([Lobos et al., 1992](#)). As a popular recreational drug in clubs (like MDMA), the activity of 2C-B and similar drugs at 5-HT_{2B} receptors should be investigated.

From 2007 onwards mephedrone (4-methylmethcathinone) became available as a popular legal alternative to MDMA ([Psychonaut Web Mapping Research Group, 2010b](#)) in the UK. Recent studies have found that this compound possesses efficacy for inducing 5-HT, noradrenaline and dopamine release ([Baumann et al., 2011](#); [Hadlock et al., 2011](#); [Kehr et al., 2011](#); [Martínez-Clemente et al., 2012](#)), rendering it something of a pharmacological chimera of amphetamine and MDMA. However, mephedrone is neither as potent as methamphetamine at inducing dopamine release, nor as potent as MDMA at inducing 5-HT release ([Baumann et al., 2011](#); [Hadlock et al., 2011](#)). Beyond the many user reports, little else is known about the pharmacology of this compound. Mephedrone has been reported to displace the 5-HT₂ antagonist ketanserin in cortical membrane preparations from rats ([Martínez-Clemente et al., 2012](#)), although the subtype selectivity for 5-HT₂ receptors is unknown, and reported hospitalisations appear to be mainly related to the amphetamine-like properties of the drug (which are considered below). Since the UK Home Office scheduled mephedrone as an illegal substance in 2010 (a move subsequently followed by regulatory authorities in many countries), some users have turned to the ever increasing number of licit alternatives, of equally uncertain pharmacology. Furthermore, such was the popularity of mephedrone with users while it was legal that many users have expressed the desire to source the drug through illegal trade ([Carhart-Harris et al., 2011](#)), and probably do despite the increased cost ([Winstock et al., 2010](#)). Finally, mephedrone is sold on the internet in different guises ([De Paoli et al., 2011](#)), which is a simple but effective ploy given the practical difficulties of test-purchasing, analysing and attempting to prosecute multiple vendors. Thus, there is a need to characterise the pharmacological properties of both mephedrone and potential molecular usurpers. NPS which appeal to this group of drug users have actions that range from fairly pure empathogenic effects to the combination of hallucinogenic- and amphetamine-like effects, often in a dose-dependent manner that users sometimes find difficult to titrate. To date, most presentations to emergency departments have been related to the latter two mechanisms of action, and are managed in much the same way as acute reactions to LSD or amphetamines.

Users of drugs with a dominant serotonin-releasing (or reuptake-blocking) profile do not consistently report symptoms consistent with acute peripheral vasoconstriction (e.g. chest pains, cold/blue fingers) nor have there been many reports in the literature of coronary or cerebral events presenting at emergency departments. It appears that at present, the potential for NPS alternatives to mephedrone has a low acute risk of 5-HT_{2A} or 5-HT_{1B} activity leading to life-threatening vasoconstriction. Therefore, the hidden risk with many available serotonergic NPS may be the chronic effect of 5-HT_{2B} receptor agonism and subsequent valvulopathy (as with MDMA), or the effect of chronic sympathetic stimulation (as with amphetamine). In recent years, the inspiration for NPS has come mostly from scientific research programmes (e.g. [Monte et al.,](#)

1997), or from the notes of Alexander Shulgin's extensive self-administration experiments, which are freely available online. As this pool of compounds is gradually made illegal, the inspiration for synthesis is likely to become more random, and potentially more dangerous. Perhaps we have been lucky not to see a resurgence in ergotism-like presentations to date.

3. Dopaminergic drugs

Dopaminergic activity is a highly sought-after property of a NPS, since compounds that induce dopamine release produce euphoric and stimulant effects via the reward system (reviewed by Ross and Peselow, 2009). Users report that some NPS produce such a powerful reward that there is a very strong urge to take further doses (so-called "fiending") until the supply of drug has run out. Ultimately, such behaviour is likely to lead to addiction and chronic use. Dopamine does not play a significant endogenous role in the cardiovascular system. However, currently abused drugs (as well as NPS, potentially) have limited selectivity and are thus likely to interfere with adrenaline/noradrenaline uptake, amongst many other actions (e.g. those that are receptor-mediated). Two of the most obvious dopamine-releasing drugs that are chronically abused – cocaine and amphetamine – cause fatalities principally via adrenergic toxicity in the cardiovascular system. Many NPS are likely to have similar toxicity since it has proven difficult to produce a selective dopamine uptake blocker (Batman et al., 2010). Drugs with effects limited to adrenergic activity appear to have little potential for abuse. Indeed, drugs with selectivity for the NET over dopamine transporters (DAT) and SERT such as the attention deficit hyperactivity disorder drug atomoxetine do not have favourable CNS effects in experienced drug users (Heil et al., 2002). As we outline below, it is the combination of the two mechanisms of action that is most probably the most toxic to the cardiovascular system: highly addictive (i.e. dopamine-releasing) sympathomimetics.

4. Adrenergic drugs

The catecholamines adrenaline and noradrenaline were also described as peripheral vasoconstrictors before their roles in the central nervous system were established (see Goldstein, 2010). Perivascular sympathetic nerves are principally noradrenergic and mediate vasoconstriction in most vascular beds via activation of alpha-adrenoceptors. Activation of the sympathetic innervation of the heart increases the rate and force of contraction via beta-adrenoceptors. Both of these effects are mimicked by circulating adrenaline released by the adrenal gland. Extreme activation of the sympathetic control of the cardiovascular system can lead to profound vasoconstriction and ischaemia. The resultant hypertension is a risk factor for strokes and myocardial infarcts, which are more common in chronic sympathomimetic abusers (see below). The cardiac effect of sympathetic stimulation produces both ischaemia (coronary vasoconstriction) and an increased oxygen demand (as a consequence of increased myocardial contractility). Most of the angina-like chest pains experienced by NPS users probably reflect such direct effects on the innervation of the heart, or central activation of the sympathetic outflow. Sympathomimetics also provoke arrhythmias which probably contribute to fatalities. As with the serotonin system, some tumours secrete predominantly catecholamines and provide clues as the likely long-term effects of sympathomimetic abuse. Thus, in pheochromocytoma, adrenal medulla-like cells proliferate and release catecholamines spontaneously. Most such tumours secrete noradrenaline or adrenaline and the effects on the cardiovascular system can be confused with CNS stimulant abuse. Left untreated, the constant stimulation of peripheral alpha- and beta-adrenoceptors by tumour-derived catecholamines leads to hypertension, ischemic heart disease, arrhythmia and cardiomyopathy (see Prejbisz et al., 2011). Unsurprisingly, chronic use of drugs which cause sympathetic nerves to release – or fail to reuptake – noradrenaline has similar pathophysiological outcomes (see

below). NPS with a similar pharmacological profile will almost certainly produce the same spectrum of cardiovascular toxic effects.

The vasoconstrictor effect of cocaine was exploited briefly as a decongestant for the treatment of asthma and rhinitis, although its addiction potential soon became apparent (see Persson, 1997). After purification and characterisation by Takemine, adrenaline came to replace cocaine as a safer remedy for life-threatening status asthmaticus and hypotensive states. Later, the longer-acting ephedrine was purified from its herbal source (Chen and Schmidt, 1924) and soon became a replacement for adrenaline for increasing blood pressure in shock, as well as a nasal and bronchial decongestant (although it has often, and probably erroneously, been considered a β -agonist bronchodilator (see Persson, 1997)). The demand for ephedrine and the limited availability of its natural source in the plant *Ephedra sinica*, in part drove the development of drugs with similar mechanisms of action such as amphetamine (Rasmussen, 2006). After the successful remarketing of amphetamine as a "pep" pill, interest in CNS activity of sympathomimetics increased. Some of the NPS that have appeared recently are compounds developed by, and subsequently rejected by pharmaceutical companies working in this area. Others are compounds selected for other effects (e.g. hallucinogenic amphetamines), but which have a sympathomimetic component. The long history of the use of cocaine, ephedrine and amphetamines can help us to predict with some certainty the chronic effects of NPS with similar pharmacodynamics properties.

After cannabis, cocaine is almost certainly the most abused illicit drug in Europe and Northern America (Degenhardt and Hall, 2011; European Monitoring Centre for Drugs and Drug Addiction, 2011). Cocaine differs from other CNS stimulants in that it not only blocks uptake of monoaminergic neurotransmitters, but it also acts as a local anaesthetic and modulator of cardiac rhythmicity via actions on voltage-gated sodium, and other channels (O'Leary and Hancox, 2009). The toxicity of cocaine is better documented than ephedrine or the amphetamines (Kloner et al., 1992; Lange and Hillis, 2001; Lange et al., 2004), but it is not always a simple task to distinguish its toxic effects via inhibition of neurotransmitter uptake versus sodium channel modulation. Approximately one quarter of patients presenting with confirmed nonfatal myocardial infarction under the age of 45 are cocaine users (Qureshi et al., 2001), although there does not appear to be a strong relationship between duration or frequency of use and this presentation (Lange and Hillis, 2001). In presentations of cocaine-related chest pain, only 6% of patients are thought to be experiencing a myocardial infarct rather than coronary vasoconstriction and myocardial ischaemia (Schwartz et al., 2010). Indeed, since autopsy of most (80%) cocaine-related deaths (i.e. those found dead) rarely reveals significant underlying cardiac pathology, it is likely that such deaths occur by coronary vasoconstriction, arrhythmia, or both. Ischaemic damage and/or infarct is not limited to the heart (although this is by far the most common presentation) and extends, for example, to the kidneys (Glauser and Queen, 2007) and gastrointestinal tract (Moghal and Melegros, 2006). As with pheochromocytoma, cardiac myopathy is also common in cocaine abusers, and may result from persistent hypertension as well as direct effects of the drug on cardiac myocytes (Kloner et al., 1992; Lange and Hillis, 2001). Incidences of strokes are higher in cocaine abusers, and are predominantly of the haemorrhagic type, probably due to hypertensive surges following drug ingestion (Treadwell and Robinson, 2007).

The exact pharmacology of ephedrine is still subject to debate. Ephedrine causes release of noradrenaline in a similar manner to amphetamine – reverse transport. Binding studies using human receptors in expression systems suggest that ephedrine binds to the NET rather than adrenergic or serotonergic receptors (Rothman et al., 2003). While some studies in rats have found that most of the cardiovascular effects of ephedrine can be accounted for by effects on sympathetic nerves (e.g. Kobayashi et al., 2003), others have found that ephedrine appears to have a direct effect on an unknown receptor(s) (e.g. Liles et al., 2006). It is not certain whether this is a species

difference, or a difference that results from the very different techniques involved in human expression systems and cardiovascular effects in rats in vivo. In addition to effects via NET, ephedrine possesses activity on DAT but has no 5-HT-releasing effect (Rothman et al., 2003). Ephedrine has a long history of comparatively safe use as a decongestant; it has also been used safely as a prescription drug for weight loss (e.g. Hallas et al., 2008). There are a few reports of psychosis induced by chronic high dose usage, especially when the drug has been taken for its CNS stimulant properties (e.g. Herridge and A'Brook, 1968) and although there are occasional reports of addiction (e.g. Miller and Waite, 2003), these are rare. The CNS stimulant side-effects of ephedrine (e.g. insomnia, hyperthermia) were apparent from its introduction and tended to reduce compliance when prescribed as decongestant bronchodilator (e.g. Christopherson and Broadbent, 1934). In the United States, ephedrine was the poor cousin to amphetamine in terms of abuse, until such stronger stimulants were controlled in 1971 (for an excellent summary see Palamar, 2011). After that time, ephedrine began appearing as an adulterant in street drugs as well as being advertised in magazines as what we might now describe as a "legal high". The effects of ephedrine abuse became clearer more recently when herbal *Ephedra* preparations entered the market as legal food supplements in the USA after a change in the law in 1994. Sold in an uncontrolled dosage, of variable quality, as a "natural" (and therefore often perceived as "safe") stimulant, widespread accidental or unknowing abuse occurred. Such supplements were popular for weight loss effects and the perceived (and unproven) ability to enhance athletic performance. Numerous reports of adverse effects matching the expected profile of sympathomimetic abuse followed: hypertension, anxiety, cardiomyopathy, stroke and myocardial infarcts (Haller and Benowitz, 2000; Naik and Freudenberg, 2004; Samenuk et al., 2002). Some have argued that causation has not been satisfactorily established in many of these cases, since ephedra-containing supplements were often formulated with other active substances such as caffeine (Soni et al., 2004). The problem of directly relating symptoms with the effects of individual substances is equally relevant at present since many users of NPS are adventurous with their drug use and often explore/exploit perceived or real synergistic pharmacodynamics actions. Furthermore, it is clear that many casual NPS users often may have little idea what substances they are ingesting, since substitutions and adulterations are commonplace and combinations of drugs are often sold as another single compound (see, for example, Spiller et al., 2011). Interestingly, ephedrine is still used as a substitute or adulterant in drugs sold on the internet (Davies et al., 2010). The less potent enantiomer of ephedrine – pseudoephedrine – remains a useful decongestant, although its amenability to chemical conversion to more potent, illicit drugs such as methamphetamine limits sales and availability in some countries. There are also occasional reports of pseudoephedrine dependence (e.g. Bharatula and New, 2011) and cardiovascular toxicities have been reported (e.g. Akay and Ozdemir, 2008; Celik, 2009; Grześk et al., 2004; Manini et al., 2005) including ischemic colitis (Dowd et al., 1999). Like the triptans, pseudoephedrine is dispensed with caution to patients who are likely susceptible to cardiovascular actions, probably limiting the number of such adverse reactions.

Although amphetamines cause reverse transport of monoamines (see Cruickshank and Dyer, 2009; Greene et al., 2008), rather than inhibition of reuptake as with cocaine, the cardiovascular toxicological profile of these drugs is similar. The data for amphetamines are poorer, and often consist of case reports or case series. Furthermore, as methamphetamine and amphetamine differ geographically in usage, the two are considered here together, and in much of the literature. In one large study in Texas, amphetamines were estimated to be associated with 0.2% of acute myocardial infarctions (Westover et al., 2008). Smaller case series suggest that up to 25% of amphetamine-related presentations with chest pain had acute coronary syndrome (summarised by Kaye et al., 2007). Amphetamine use is also associated with cardiomyopathy, coronary artery disease, aortic dissection and

sudden death (likely to be due to arrhythmia; Kaye et al., 2007). Notably (and as is the case with ephedrine) when amphetamines are used chronically at therapeutically-useful doses (as in treatment of attention deficit hyperactivity disorder) no clear evidence for toxicity is apparent (Habel et al., 2011). From the mid to late 1990s benzylpiperazine (BZP) became a popular legal substitute for amphetamines in several countries (Arbo et al., 2012), although it has subsequently been banned by many authorities. Benzylpiperazine preferentially inhibits NET, with slightly lower affinity for DAT and is a hundred fold less active at SERT (Negus et al., 2009). As such, BZP mimics the effects of amphetamine fairly closely, and users present to emergency departments with a similar sympathomimetic toxidrome (summarised by Arbo et al., 2012). Indeed, experienced users cannot distinguish the effects of BZP from amphetamine (see Hill and Thomas, 2011). Combinations of BZP with serotonergic piperazines such as mCPP or TMPP have become popular substitutes for MDMA.

The leaves of Khat (*Catha edulis*) are chewed for their stimulant effects in Yemen and some East African countries. The principle active ingredient in Khat is cathinone, which is structurally closely related to amphetamine and acts in a similar manner as a substrate for the DAT and NET (Baumann et al., 2011). Khat chewing has been associated with the typical toxic syndrome of chronic sympathomimetic abuse (Al-Motarreb et al., 2010) and has been found to be a risk factor for acute myocardial infarction in a dose-dependent manner (Al-Motarreb et al., 2005). The recent popularity of the synthetic cathinone-derivative mephedrone can probably be ascribed to the combined DAT and SERT inhibitory activity (see above) of this compound. While not as potent as methamphetamine, mephedrone also causes noradrenaline release (Baumann et al., 2011) from which we would predict a sympathomimetic toxicological profile. A survey of users indicates that most (73%) would prefer to take MDMA (with its superior SERT selectivity) to mephedrone (Carhart-Harris et al., 2011). Thus, mephedrone is a second-rate substitute for MDMA (probably due to the NET/DAT effects), but still a desirable drug of abuse in some circles. Despite being banned in the UK, it is still sold on the internet (De Paoli et al., 2011), highlighting the difficulties of policing online vendors. In terms of cardiovascular toxicity, the few available reports suggest that the amphetamine-like properties of mephedrone (principally anxiety, tachycardia, palpitations and hypertension) led to emergency room presentations (Regan et al., 2010; Wood et al., 2011a). It has been suggested that, at the time of these studies, users were more willing to seek medical assistance since the drug was legal (Regan et al., 2010), so this profile of acute effects is probably fairly representative. The chronic cardiovascular effects of mephedrone are not likely to become apparent unless a significant number of users gain access to reliable, pure source of the drug, but could be predicted upon the basis of effects on NET and 5-HT₂/alpha-adrenoceptor receptors, once functionally established. Approximately one-fifth of mephedrone users report discoloration of fingers/joints (Carhart-Harris et al., 2011) – suggesting vasoconstriction – which may reflect 5-HT₂ receptor-mediated effects predicted from animal studies (Martínez-Clemente et al., 2012). However, these potential vasoconstrictor effects may also relate to the amphetamine-like qualities of mephedrone. After the ban on mephedrone, a variety of other cathinone derivatives and other "me too" compounds with similar activity (generally sold as "bath salts") emerged onto the market, all with sympathomimetic toxicities that led to presentations to hospitals (see Hill and Thomas, 2011; Prosser and Nelson, 2011; Spiller et al., 2011). Of these more recent stimulants, methylenedioxypyrovalerone (MDPV) has caused particular concern with authorities and users for its sympathomimetic profile and tendency to cause re-dosing. Although there have been many close calls with MDPV toxicity, there has only recently been a death associated with use of this drug alone (Murray et al., 2012). The UK Home Office recently banned another stimulant, desoxypipradrol which was found to be ten times more potent than cocaine at releasing dopamine in rat brain slice preparations (Davidson and Ramsey, 2012). This compound produces an unusual response

consisting of a brief “high” (with possible sympathomimetic effects), after which patients have been admitted to hospital suffering from extended periods (3–5 days) of insomnia and paranoia but with normal cardiovascular parameters (Wood et al., 2011b). These longer-lasting effects may be due to a metabolite with a long half-life and less affinity for NET.

5. Conclusions

Reports of adverse cardiovascular complications of NPS are beginning to appear in the literature. For these reasons, it is important to fully investigate the cardiovascular pharmacology of NPS as they become available and subsequent to their regulation (since this rarely influences demand). As the pool of chemical structures in the literature is slowly mined, vendors are likely to turn to less other compounds that may not have been examined *in vitro* or *in vivo*. It is clear from the history of psychoactive drug use that two particular effects of NPS may lead to cardiovascular complications:

1. Drugs with affinity for the 5-HT_{2B} receptor, which are likely to cause heart valvulopathy. The history of MDMA use shows that even weekly use of such drugs is likely to cause pathology if taken for several years.
2. Drugs which can inhibit noradrenaline uptake, or cause reverse transport. These drugs are the most likely to cause the sympathomimetic toxic syndrome that cocaine and amphetamine produce.

Drugs which have addiction liability are likely to increase the likelihood of chronic use and cardiovascular pathology. The affinity of NPS for receptors coupled to vasoconstriction (5-HT_{2A}, 5-HT_{1B}, and alpha-adrenoceptors) is also an important determinant of the liability to cause tissue ischemia.

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